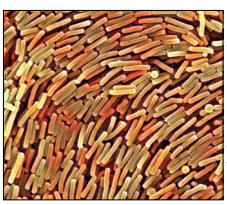
Expanding the armamentarium for the treatment of *Clostridium difficile* infection



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In *The Lancet Infectious Diseases*, Richard Vickers and colleagues[1] report results of a phase 2 study of ridinilazole, a promising new drug for the treatment of *Clostridium difficile* infection. Although efforts to improve infection control practices and antimicrobial stewardship have led to significant reductions in some countries,[2] *C difficile* infection remains a substantial problem worldwide.

All-cause 30-day mortality associated with *C difficile* infection has been reported to be in the region of 9–38%.[3,4] Furthermore, cases are associated with excess length of hospital stay of approximately 7 days (and 12 days in severe cases).[3] *C difficile* infection usually occurs following disruption of the intestinal microbiota resulting from exposure to antibiotics. The risk of *C difficile* infection increases by up to six times during antibiotic therapy and in the month thereafter.[5,6]

Risk of disease recurrence within 8 weeks of treatment of an initial episode is estimated to be approximately 15–25%; for those with more than one previous recurrence, the risk of further recurrences increases to 40–65%.[7,8] Recurrences have been associated with impaired immune responses to *C difficile* toxins together with disturbance of the indigenous colonic microbiota. Continued use of antibiotics, as well as numerous other factors such as concomitant anti-ulcer medication and older age (particularly those older than 65 years) are well recognised risk factors for recurrence.[7] Management of such patients is challenging and places substantial demand on health-care resources.

For several decades the only available drugs to treat *C difficile* infection were metronidazole and vancomycin. Concerns over emerging resistance and worsening clinical outcomes have resulted in a shift away from the use of metronidazole, even for non-severe cases.[9,10] Fidaxomicin was licensed in the European Union and USA in 2011. Its use has led to significant reductions in recurrences compared with the use of vancomycin, particularly when it is not restricted to highly selected cases.[11] Despite its effectiveness for all *C difficile* infections, fidaxomicin is generally used to treat a first recurrence; this decision is probably driven by the greater cost of the drug compared with vancomycin. However, this strategy could be short-sighted since the costs of managing recurrent episodes can be severe.[12]

Because of the limited number of effective antimicrobials available to treat *C difficile* infection, the development of new drugs is vital. An ideal agent would be bactericidal against vegetative cells, inhibit spore and toxin production, have targeted activity against *C difficile* while sparing indigenous gut flora, be poorly absorbed from the gastrointestinal tract, and be well tolerated. Ridinilazole appears to have many of these attributes, making it a good candidate for further development.

The main outcome measure reported by Vickers and colleagues[1] was sustained clinical response. This is a combined endpoint that measures cure at the end of treatment (resolution of symptoms with three or fewer unformed bowel movements over a 24-h period) and an absence of recurrence in the 30 days after treatment. 24 (66·7%) of 36 patients in the ridinilazole group had a sustained clinical response compared with 14 (42·4%) of 33 patients in the vancomycin group, showing statistical superiority in the modified intention-to-treat analysis. Subgroup analysis of this outcome measure showed that ridinilazole performed better than vancomycin in patients older than 75 years, those with markers of severe disease, those with one or more episodes of *C difficile* infection, and those requiring concomitant antibiotics, although the differences were not all statistically significant because of the low numbers. Recurrence of infection occurred in four (14·3%) of 28 ridinilazole-treated participants versus eight (34·8%) of 23 vancomycin-treated participants.

The study was somewhat limited by the inclusion of patients who were slightly younger than those who might be expected to be seen in everyday clinical practice (most patients were younger than 65 years). Similarly, only 10% in the ridinilazole group and 8% in the vancomycin group had a previous episode of *C difficile* infection, and just 14% in the ridinilazole group and 18% in the vancomycin group had severe disease. Furthermore, it is unclear why some of the centres were not able to recruit to the study (only 21 of 33 [64%] sites recruited patients). Discounting these shortcomings, it is rare for a study of an antimicrobial to show statistical superiority over the standard of care.

The main advantage of ridinilazole and other new drugs such as fidaxomicin and bezlotoxumab appears to be related to the reduction or prevention of recurrence. Therefore, the development of bedside tools that can be used in real time to predict accurately the risk of recurrent *C difficile* infection could be helpful. These tools could help to optimise treatment for those at risk of severe, complicated, or recurrent infection at the early stages of disease and drive improvement in a range of clinical outcomes.

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